

### **REMARKS**

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and remarks.

#### **Status of the Claims**

Claims 24, 27, 29, 31, 33 and 38 are pending and presented for examination. No new matter is added.

#### **Rejections under 35 U.S.C. § 103**

Claims 24, 27, 29, 31, 33 and 38 are rejected under 35 U.S.C. § 103(a) as allegedly obvious over EP 001167388 (“the ‘388 publication”) and in view of Sato *et al.* (*Cancer Research*, 1993), as is evidenced by the specification under Example 1. Office Action, item 5, pages 2-4. Specifically, the PTO alleges “The ‘388 publication teaches and claims a single-chain Fv which is a humanized single-chain Fv capable of inducing apoptosis of cells having Integrin Associated Protein (IAP). An H and L chain V region of MABL-2 which is a humanized L chain V region (see published claims 4-5 and 10-11 and SEQ ID NOs: 7-8).” *Id.* at page 2. In so citing, the PTO alleges “The reference teachings differ from the claimed invention only in the recitation of specific human heavy and light framework in claims.” *Id.* at page 3.

Turning to Sato, the PTO alleges “Sato *et al.* teach the creation of a reshaped human antibody that is equivalent to the original mouse antibody in terms of binding and inhibition.” *Id.* at page 3. In so doing, Sato allegedly teaches two versions (designated version a and version b) for reshaped PM-1 light chain variable regions, and six versions (designated version a through version f) for reshaped PM-1 heavy chain variable region. *Id.*

While admitting “Sato *et al.* do not teach humanizing the MABL-2 specific antibodies of the instant invention,” the PTO alleges that “it would have been obvious to humanize any antibody intended for therapeutic uses in humans.” *Id.* Further, the PTO alleges “The resultant humanized MABL-2 antibody would comprise the claimed FRs. The resultant humanized antibodies would comprise the claimed sequences as is evidenced by the

specification under Example 1....” *Id.* Applicants respectfully traverse the grounds for this rejection.

In order to validate a conclusion that a claim would have been obvious, the PTO must show that all recited elements of the claim were evidenced in the art. Further, the PTO must demonstrate that one of ordinary skill in the art could have combined the elements in the manner claimed, via known methodology, with no change in the respective function(s) of the elements and with the resultant combination yielding nothing more than predictable results. *KSR v. Teleflex*, 127 S. Ct. 1727, 1739 (2007).

If any of these requirements do not pertain, then the PTO is barred from concluding that the claim in question would have been obvious. Such is the case here.

While the ‘388 publication may allegedly disclose a single-chain antibody derived from MABL-2, the ‘388 publication neither teaches nor suggests a humanized antibody binding to CD47. For this reason alone, ‘the ‘388 publication could not render the present claims obvious.

To the extent that Sato *et al.* discloses methodology for reshaping a human antibody with CDR grafting, Sato’s methodology entails selecting human antibodies having similar variable regions to a mouse antibody and replacing the mouse FR region with one from a human antibody. Sato *et al.* selected the FR region of REI, a member of human kappa light chain subgroup I, for the light chain and VAP, a member of human heavy chain subgroup II, for the heavy chain. In reshaping the light chain, Sato *et al.* generated two versions, version “a” and version “b.” In version “a,” the FR regions correspond to those in the humanized Campath antibody. In version “b,” a phenylalanine at position 71 in FR3 was replaced with tyrosine. Version “b” virtually abolished binding to the antigen. *See* Sato, e.g., page 852, 2<sup>nd</sup> column, 2nd paragraph.

Likewise, in reshaping the heavy chain, six versions of the heavy chain were designed, wherein each version had different single amino acid replacements at different positions. Version “f” showed the best antigen binding, having site mutations at position 27, 28, 29, 30

and 71. Version “a” showed poor binding, despite sharing site mutations at positions 27 and 30 with version “f.”

Thus, Sato *et al.* teaches that certain amino acid residues in the FR region are important for antigen binding and that one cannot predict which residues will influence or control antibody activity. For this reason alone, Sato *et al.* does not support the PTO’s position that it would have been obvious and “straightforward” to produce a humanized antibody binding to CD47.

Furthermore, the Federal Circuit has made clear that obviousness rejections are viewed as not being supported by mere conclusory remarks. “If the examiner is able to render a claim obvious simply by saying it is so, neither the Board nor this court is capable of reviewing that determination. *See KSR*, 550 U.S. at 418, citing *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006). Thus, the PTO must proffer more than its mere conclusory allegation that one could start from the ‘388 publication and arrive at the instant humanized antibodies because Applicants’ own specification allegedly discloses “in a humanized MABL-2 antibody H chain (version “1.1”), FR1 to FR4 were identical with FR1-FR4 of the human antibody AF216824, and the CDRs were identical with the CDRs in the H chain V region of the mouse MABL-2.” *Id.* at page 3, citing Applicants’ specification, published paragraph number [0075].

Not only does the PTO’s stated position appear conclusory and based on impermissible hindsight, but the PTO’s position is factually inaccurate. To clarify, Applicants’ H chain is not identical with version “1.1” and the positions of the modifications are neither taught nor suggested by either the ‘388 publication or Sato *et al.* Furthermore, and as taught by Sato *et al.*, a site mutation can lead to any of an increase in activity, decrease in activity, or no change. *See, e.g., Sato et al.*, version “b” of the light chain. Therefore, Sato *et al.* could not remedy the ‘388 publication’s deficiencies to produce Applicants’ antibody having specific sequences that are superior to other humanized MABL-2 antibodies. *See, e.g., Figures 6-11.*

Accordingly, no permissible combination of the '388 publication and Sato *et al.* would render claims 24, 27, 29, 31, 33 and 38 obvious. Thus, Applicants respectfully request the rejection be withdrawn.

**CONCLUSION**

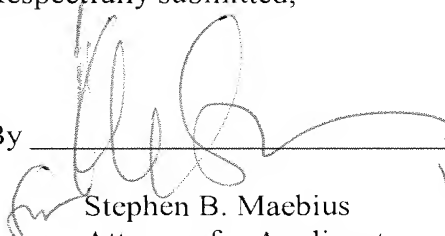
Applicants believe that the present application is in condition for allowance, and request an early indication of same.

The Examiner is invited to telephone the undersigned if an interview would advance prosecution.

Respectfully submitted,

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